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WO 2005/066867 A3

(54) Title: MODULATORS OF CELL-SURFACE RECEPTORS OF THE Ig-CLASS

(57) Abstract: Method of identifying a modulator of CD28 comprising comparing a structural model of a candidate modulator with a structural model of CD28 to thereby determine whether the modulator will bind to CD28, wherein the structural model is derived from, or comprises, structural coordinates of a crystal of: (i) CD28, (ii) a fragment of CD28, or (iii) a homologue of (i) or (ii). The crystal of CD28 in a soluble form complexed with the Fab fragment of a mitogenic (superagonistic) antibody has been obtained and used for the determination of the 3D-structure of the receptor. The application also relates to modulators of superagonistic signalling for any receptor of the CD28 family, i.e. to superagonistic antibodies and chimeric proteins thereof, and to the screening of the superagonistic modulators. In the methods of screening, the binding of the candidate modulators to a portion of the receptor proximal to the cell membrane is investigated.

INTERNATIONAL SEARCH REPORT

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| Intern: | Application No |
| PCT/GB2005/000099 | |

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| A. CLASSIFICATION OF SUBJECT MATTER | | |
| IPC 7 | G06F19/00 | C07K14/705 C07K16/28 |

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| According to International Patent Classification (IPC) or to both national classification and IPC |
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| B. FIELDS SEARCHED |
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| Minimum documentation searched (classification system followed by classification symbols) |
| IPC 7 G06F C07K |

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| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched |
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| Electronic data base consulted during the international search (name of data base and, where practical, search terms used) |
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| EPO-Internal, WPI Data, PAJ |
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| C. DOCUMENTS CONSIDERED TO BE RELEVANT |
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| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 03/095487 A (ISIS INNOVATION LIMITED; CERUNDOLO, VINCENZO; GADOLA, STEPHAN) 20 November 2003 (2003-11-20) abstract; claims 15,31,39-53 | 10-15 |
| Y | ----- STAMPER CARIN C ET AL: "Crystal structure of the B7-1/CTLA-4 complex that inhibits human immune responses" NATURE (LONDON), vol. 410, no. 6828, 29 March 2001 (2001-03-29), pages 608-611, XP002328138 ISSN: 0028-0836 abstract; figure 3 ----- | 1-15,17, 18,32 |
| X | ----- -/- | 10-15 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- *P* document published prior to the International filing date but later than the priority date claimed

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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- *&* document member of the same patent family

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016 | Fausti, S |
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INTERNATIONAL SEARCH REPORT

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| Internal | Application No |
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C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | LÜHDER F ET AL: "Topological requirements and signaling properties of T cell-activating, anti-CD28 antibody superagonists" JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP, vol. 197, no. 8, 21 April 2003 (2003-04-21), pages 955-966, XP002261827 ISSN: 0022-1007 cited in the application abstract; figures 1-5; page 959, right-hand column, line 3 - page 961, left-hand column, line 17; page 962, paragraph joining left- and right-hand columns; page 963, right-hand column, last paragraph ----- | 35 |
| Y | abstract; figures 1-5; page 959, right-hand column, line 3 - page 961, left-hand column, line 17; page 962, paragraph joining left- and right-hand columns; page 963, right-hand column, last paragraph ----- | 1-15, 17, 18, 32 |
| X | WO 03/078468 A (TEGENERO AG; HUENIG, THOMAS) 25 September 2003 (2003-09-25) | 35 |
| Y | abstract; page 1, lines 24-29; paragraph joining pages 1 and 2; page 4, line 16 - page 5, line 21; page 7, last paragraph; page 19, first paragraph; claims 1-3, 5; figures 2, 5, 6, 15-17; Seq. IDs 1-7 ----- | 1-15, 17, 18, 32 |
| T | LINSLEY PETER S: "New look at an old costimulator." NATURE IMMUNOLOGY. MAR 2005, vol. 6, no. 3, March 2005 (2005-03), pages 231-232, XP002328139 ISSN: 1529-2908 ----- | |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/000099

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 16 because they relate to subject matter not required to be searched by this Authority, namely:
Claims 34 and 35 are directed to a method of treatment of the human/animal body. The search could only be carried out and based on the alleged effects of the therapeutically active compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

See annex

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-18 and partially claims 32, 35.

Crystal structure of CD28 and its use in the screening of CD28 modulators. Claims 32 and 35 are to be considered within this group in so far as they only relate to the method of claims 1-9.

2. claims: 19, 20, 25-34 and partially claims 22-24, 35.

Superagonistic modulators of membrane receptors having an intracellular domain dependent on an extrinsic protein kinase, wherein the modulator binds to an extracellular domain of the receptor which is proximal to the cell membrane; peptides corresponding to said extracellular domains; screening methods for the identification of the superagonistic modulators and their medical uses. With respect to claim 34, it is considered that the steric effect, on which the claimed method is based, is inherent the binding of the modulating agent to the membrane-proximal domain. Accordingly, claim 34 has been incorporated in this group.

3. claims: 21 and partially claims 22-24, 35.

Chimeric proteins inducing a superagonistic signalling by membrane receptors having an intracellular domain dependent on an extrinsic protein kinase, wherein the chimeric proteins consist of two Fv antibody regions; their medical uses.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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|-------------------|-----------------|
| Internal ref. | Application No. |
| PCT/GB2005/000099 | |

| Patent document cited in search report | | Publication date | | Patent family member(s) | | Publication date |
|--|---|------------------|----------------------|---|--|--|
| WO 03095487 | A | 20-11-2003 | AU | 2003227935 A1 | | 11-11-2003 |
| WO 03078468 | A | 25-09-2003 | AU DE EP US | 2003221604 A1 10212108 A1 1483293 A2 2004092718 A1 | | 29-09-2003 02-10-2003 08-12-2004 13-05-2004 |